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FISH & RICHARDSON P.C. (BO)			EXAMINER	
P.O. BOX 1022			ANGELL, JON E	
MINNEAPOLIS, MN 55440-1022				
			ART UNIT	PAPER NUMBER
			1635	
			NOTIFICATION DATE	DELIVERY MODE
			03/08/2011	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/587,775	<b>Applicant(s)</b> ELMEN ET AL.	
	<b>Examiner</b> J. E. ANGELL	<b>Art Unit</b> 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 14 December 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 30-57 is/are pending in the application.
- 4a) Of the above claim(s) 33-39, 41-43, 49-53 and 55 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 30-32, 40, 44-48, 54, 56 and 57 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/15/06 3/15/09 9/15/13</u>                                  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

This Action is in response to the communication filed on 12/14/2010.

Claims 30-57 are currently pending.

### **Election/Restrictions**

Applicant's election with traverse of the species: LNA, position 14, RNA nucleobase, and phosphate internucleotide linkage in the reply filed on 12/14/10 is acknowledged. The traversal is on the ground(s) that consideration of the other species will make prosecution more compact. This is not found persuasive because making prosecution more compact is not a criterion in determining validity of an election requirement. It is noted, however, that should the elected species be found allowable, the non-elected species will be considered for rejoinder.

The requirement is still deemed proper and is therefore made FINAL.

Claims 33-39, 41-43 49-53 55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/14/10.

Claims 30-32, 40, 44-48, 54, 56, 57 are examined herein, as they are drawn to the elected invention

Art Unit: 1635

### **Claim Rejections - 35 USC § 102**

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 30-32, 40, 44-48, 54, 56, 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Braasch et al. (Biochem. 2003, cited by Applicant).

3. It is noted that the elected species for location of the modified nucleotide is position 14. It is also noted that none of the instant claims are explicitly limited to having the modification at position 14 (e.g., claim 30 encompasses having a modification at any of positions 8-14).

Searching the prior art, no references were found which taught the elected species (e.g., LNA at position 14); however, the instant reference does teach having the elected modification (LNA) at a position within the range of position encompassed by the claims (e.g., position 13). Since it is clear that the reference applies as 102 art over non-elected species which are claimed, the reference is applied here as a 102 reference against the claimed (but non-elected) embodiments which it teaches. It is also noted that the reference is also used in a 103 rejection (below) against the elected species which the references does not explicitly teach.

4. Braasch et al. teach siRNAs that can be 21 nucleotides in length which can comprise chemical modifications, including locked nucleic acids (LNA), in either the sense or antisense strands that impart increased potency, stability and/or pharmacokinetic properties (e.g., see

Art Unit: 1635

abstract, Fig. 7, etc.). At Figure 7, Braasch et al. teach a number of different specific siRNAs having one or more LNA modifications at various locations throughout the siRNA molecule, and explicitly teach a siRNA having a LNA at positions 8 and 13 from the 5'-end (e.g., see Fig. 7, siRNA identified as "L3 and "L5"). At Figure 7, Braasch et al. teach that the LNA has a structure that is encompassed by the structure of the beta-D-oxy-LNA shown in the specification as Scheme 2(2A) and Scheme 3(2A). It is noted that the claims explicitly encompass a siRNA comprising the LNA 8-14 nucleotides from the 5'-end of the sense strand (e.g., see claim 30). Since Braasch et al teach that the siRNA has LNAs at the positions 8 and 13 from the 5' end, to the extent that the claims read one these specific embodiments, Braasch et al. anticipate the instant claims.

5. Claims 30-32, 40, 44-48, 54, 56, 57 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. 2005/0261212 (McSwiggen et al.).

6. It is noted that the elected species for location of the modified nucleotide is position 14. It is also noted that none of the instant claims are explicitly limited to having the modification at position 14 (e.g., claim 30 encompasses having a modification at any of positions 8-14). Searching the prior art, no references were found which taught the elected species (e.g., LNA at position 14); however, the instant reference does teach having the elected modification (LNA) at a position within the range of position encompassed by the claims (e.g., positions 8-10). Since it is clear that the reference applies as 102 art over non-elected species which are claimed, the reference is applied here as a 102 reference against the claimed (but non-elected) embodiments

Art Unit: 1635

which it teaches. It is also noted that the reference is also used in a 103 rejection (below) against the elected species which the references does not explicitly teach.

7. McSwiggen et al. teach siRNAs that can be 19 to 23 nucleotides in length which can comprise chemical modifications in either the sense or antisense strands that impart increased stability and/or nuclease resistance (e.g., see claims including claim 37-46). At paragraph 63 McSwiggen et al. teach that the siRNAs can comprise one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid nucleotides at the 5'-end, 3'-end, 5' and 3'-end, or any combination thereof. At paragraph 163 McSwiggen et al. teach that the locked nucleic acid nucleotides are 2', 4'-C methylene bicyclo nucleotide (and refer to WO 99/14226, Wengel et al. as an example (note: Wengel et al. is cited by Applicant). The 2', 4'-C methylene bicyclo nucleotide referred to by McSwiggen et al. is encompassed by the structure of the beta-D-oxy-LNA shown in the specification as Scheme 2(2A) and Scheme 3(2A). It is noted that the claims explicitly encompass a siRNA comprising the LNA 8-14 nucleotides from the 5'-end of the sense strand (e.g., see claim 30). Since McSwiggen et al teach that the siRNA can contain up to 10 LNAs at the 5' or 3' end, the reference necessarily teaches an siRNA that would have the LNA at the first 10 positions from the 5'-end. Thus, to the extent that the claims read one these specific embodiments, McSwiggen et al. anticipate the instant claims.

### **Claim Rejections - 35 USC § 103**

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

Art Unit: 1635

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 30-32, 40, 44-48, 54, 56, 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braasch et al. (Biochem. 2003, cited by Applicant).

11. As indicated above, the elected species for the position of the LNA modification is position 14 from the 5'-end. The instant rejection is applies to the instant claims to the extent that they are drawn to the elected species.

12. The teachings of Braasch et al. as it applies to the claims in the instant rejection are indicated above.

13. Braasch et al. do not specifically teach that the LNA modification is located at position 14 from the 5'-end of the sense strand of the siRNA molecule.

14. However, Braasch et al. demonstrate that LNA modifications can be placed throughout the sense and antisense strands of a siRNA molecule without diminishing efficacy. Furthermore, Braasch et al. specifically teaches,

“These data suggest that LNA substitutions are well-tolerated and can lead to large increases in T<sub>m</sub> values. However, to maximize the likelihood that potent inhibition of gene expression will be maintained, LNA substitutions should be kept to a minimum and should not infringe on the central region of the RNA. It is not difficult to meet these

Art Unit: 1635

criteria since only modest numbers of LNA substitutions are necessary to significantly increase T<sub>m</sub>.”

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time of invention, that the siRNA oligonucleotide of Braasch et al. could be modified such that it comprised LNA at position 14 from the 5'-end of the sense strand, with a reasonable expectation of success.

See the Supreme Court decision in *KSR International CO. v. TELEFLEX INC.*, No. 04-1350 (U.S. Apr. 30, 2007). Also, at page 13, the Court stated, “If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” At page 15, the Court expressed, “The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patent. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way.” At page 17, the Court expressed “When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.” (emphasis added)

Since the skills required to make the LNA modification at position 14 were within the technical grasp of one of ordinary skill in the art at the time of the invention, it would have been obvious to one of ordinary skill in the art to perform routine optimization using the known



Art Unit: 1635

oligonucleotide chemical modification to arrive at the claimed siRNA. See *In re Aller*, 105 USPQ 233 at 235, which teaches that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Routine optimization is not considered inventive and in the instant case, no evidence has been presented that the selection of position 14 for the LNA was other than routine, or that the products having LNA at position 14 has any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. Further, considering that Braasch et al. provides guidance which clearly indicates that LNA modification should not be in the central region of siRNA, there would have been motivation to place the LNA near the end of the siRNA, and position 14 of a 21 nucleotide would be at a position expected to result in a functional siRNA, based on the fact that Braasch et al indicates that modification at position 13 results in a functional siRNA (e.g., see Figs. 7-8, etc.).

15. Claims 30-32, 40, 44-48, 54, 56, 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 2005/0261212 (McSwiggen et al.).

16. As indicated above, the elected species for the position of the LNA modification is position 14 from the 5'-end. The instant rejection is applies to the instant claims to the extent that they are drawn to the elected species.

17. The teachings of McSwiggen et al. as it applies to the claims in the instant rejection are indicated above.

Art Unit: 1635

18. McSwiggen et al. do not specifically teach that the LNA modification is located at position 14 from the 5'-end of the sense strand of the siRNA molecule.

19. However, McSwiggen et al. teach that functional siRNA can comprise LNA modification throughout the siRNA, including explicitly teaching that there can be "10 or more" modifications at the 5'-end, 3'-end, or both ends.

See the Supreme Court decision in *KSR International CO. v. TELEFLEX INC.*, No. 04-1350 (U.S. Apr. 30, 2007). Also, at page 13, the Court stated, "If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." At page 15, the Court expressed, "The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patent. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way." At page 17, the Court expressed "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." (emphasis added)

Since the skills required to make the LNA modification at position 14 were within the technical grasp of one of ordinary skill in the art at the time of the invention, it would have been obvious to one of ordinary skill in the art to perform routine optimization using the known

Art Unit: 1635

oligonucleotide chemical modification to arrive at the claimed siRNA. See *In re Aller*, 105 USPQ 233 at 235, which teaches that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Routine optimization is not considered inventive and in the instant case, no evidence has been presented that the selection of position 14 for the LNA was other than routine, or that the products having LNA at position 14 has any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

### **Conclusion**

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. ANGELL whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1635

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. ANGELL/

Primary Examiner, Art Unit 1635